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Dectin-1: a role in antifungal defense and consequences of genetic polymorphisms in humans

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Abstract The clinical relevance of fungal infections has increased dramatically in recent decades as a consequence of the rise of immunocompromised populations, and efforts to understand the underlying mechanisms of protective immunity have attracted renewed interest. Here we review Dectin-1, a pattern recognition receptor involved in antifungal immunity, and discuss recent discoveries of polymorphisms in the gene encoding this receptor which result in human disease.

Introduction

The immune system of mammals and other vertebrates is characterized by two interrelated components, the innate and adaptive responses, both of which are required for the resolution of most infections. The innate immune system comprises cells such as macrophages, neutrophils, and dendritic cells, which are broadly distributed throughout the body, including at portals of pathogen entry, and are involved in the initial capture and presentation of microbial antigens. The field of innate immunology was revolutionized by Charlie Janeway Jr. with the theory of pattern recognition, which proposed that conserved structures of infectious organisms (the pathogen associated molecular patterns or PAMPs) were recognized by the immune system through a set of specialized germline-encoded receptors (the pattern recognition receptors or PRRs). Janeway's theory not only suggested a general principle of innate immune recognition, it also provided a foundation for the current understanding of how it connects with the adaptive immune system (Medzhitov 2009). Accordingly, the field of immunology has witnessed the discovery of many different PRRs over the last few years, some of which can induce cellular responses and initiate the adaptive arm of the immune system. The adaptive response involves specific recognition of microbial antigens by lymphocyte receptors resulting in clonal expansion, cellular differentiation, the production of specific antibodies, and the development of immunological memory. Here we review recent insights regarding the innate recognition and response to fungal infections. We focus in particular on Dectin-1, a PRR that we and others have shown is important in antifungal defense in humans and mice. However, although beyond the scope of this review, the reader is reminded that there are also several polymorphisms in other genes (such as *MBL* and *STAT3*, for example) that have been linked with susceptibility to fungal infections (for reviews see Antachopoulos et al. 2007; Carvalho et al. 2010).

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Pattern recognition receptors in cellular responses against fungal infections

PRRs can be broadly categorized based on their cellular expression—on the cell surface, in intracellular compartments, or secreted into the serum or tissue fluids; these groups can be further subdivided into families based on structure and function. PRRs account for the quick

responses of innate immunity because once they recognize a PAMP, the PRR-expressing effector cells function immediately rather than after they have undergone somatic recombination and proliferation, as occurs in adaptive immunity. PRRs activate effector cells by driving key cellular functions, and the most important and widely studied PRRs in terms of fungal recognition are Toll-like receptors (TLRs) and C-type lectin receptors (CLRs).

Toll-like receptors

The TLR proteins are characterized by extracellular leucine-rich repeat motifs that are involved in ligand recognition. They also possess a cytoplasmic Toll/interleukin (IL-1) receptor (TIR) domain, which mediates intracellular signaling. Toll was first discovered in *Drosophila melanogaster* as a cell surface receptor involved in the regulation of development and subsequently shown to function in immunity (Hashimoto et al. 1988; Lemaitre et al. 1996). To date, 10 and 12 TLRs have been identified in humans and mice, respectively. Most TLRs have now been demonstrated as having PAMP "ligands," including lipoproteins, lipids, proteins, and nucleic acids derived from a wide variety of microorganisms (Akira et al. 2006). Ligand recognition by TLR homo- or heterodimers leads to the recruitment of intracellular adaptors such as MyD88, Mal (also called TIRAP), TRIF, and TRAM. This activates signaling cascades that ultimately trigger transcription factors and induce TLR-specific patterns of gene expression and the production of various cytokines and chemokines.

A role for TLRs in antifungal defense was first suggested by the increased susceptibility of Toll-deficient *Drosophila* to infection with *Aspergillus fumigatus* (Lemaitre et al. 1996). It has since been shown that mice lacking the TLR adaptor MyD88 are highly susceptible to fungal infections, including *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* (Netea et al. 2006). The precise fungal ligands detected by TLRs are not very well characterized; however, it is known that phospholipomannans are recognized by TLR2 and glucuronoxylomannans and mannans are recognized by TLR4 (Netea et al. 2008).

It transpires that the involvement of individual TLRs in antifungal immunity is not as clear-cut as with the MyD88 adaptor, as conflicting results have been reported by different research groups. For example, initial studies suggested that TLR4-deficient mice were more susceptible to disseminated candidiasis. Other studies using models of intragastric infection or intravenous reinfection also showed that $TLR4^{-/-}$ mice were more susceptible to *C. albicans* (Bellocchio et al. 2004). In contrast, $TLR4^{-/-}$ mice were equally susceptible as wild-type mice in models of intravenous infection with *C. albicans* yeast (Murciano et al. 2006), and even survived longer in a model of intravenous infection with *C. albicans* hyphae (Bellocchio et al. 2004). A recent investigation that used a panel of different *C. albicans* strains suggests that TLR4 is important for the recognition of some, but not all, strains of *C. albicans* (Netea et al. 2010), and this variability in recognition is likely to account for the differences observed in the above studies. TLR2, TLR9, TLR1, and TLR6 have also been implicated in the recognition and response to fungal pathogens (Carvalho et al. 2010; van de Veerdonk et al. 2008). Although the precise contributions of individual TLRs is still unclear, an integrated model of fungal recognition involving TLRs and C-type lectins has been proposed and highlights the complex interaction that occurs between host PRRs and invading pathogens (Netea et al. 2008).

There are associations between genetic variations in TLRs and fungal diseases in humans (for review see Carvalho et al. 2010). For example, polymorphisms in *TLR4* have been associated with susceptibility to invasive aspergillosis in certain transplant recipients and chronic cavitary pulmonary aspergillosis. Furthermore, *TLR4* polymorphisms were shown to contribute to a higher risk of systemic *Candida* infection. An association between a *TLR9* polymorphism and the development of allergic bronchopulmonary aspergillosis has also been reported. A global role of TLRs in host defense against fungal infections in humans, however, has been questioned by clinical observations that patients with a defect in MyD88 are not any more susceptible to fungal infections than the normal population (von Bernuth et al. 2008).

C-type lectin receptors

A noteworthy discovery in the field of innate immunology was the identification of C-type lectin receptors (CLRs) with the ability to induce intracellular signaling. These receptors have been divided into 17 groups, but of relevance here are the myeloid-expressed CLRs belonging to the Group II, V, and VI subgroups (Zelensky and Gready 2005). A number of these receptors, namely, DC-SIGN, the mannose receptor, Dectin-1, and Dectin-2, function in the recognition of fungal pathogens and have been reviewed elsewhere (Willment and Brown 2008). Of these receptors, Dectin-1 is the most extensively studied in terms of a role in fungal disease and is the focus of the remainder of this review.

Dectin-1

Structure and expression

Dectin-1 consists of a single extracellular C-type lectin-like domain (CTLD), a transmembrane region, and a

cytoplasmic tail that contains a single tyrosine-based activation motif (Fig. 1). In both humans and mice, alternative splicing generates two major Dectin-1 isoforms and a number of minor isoforms (Heinsbroek et al. 2006; Willment et al. 2001). The two major isoforms, which are the only isoforms functional for β-glucan binding, differ with regard to the presence or absence of a stalk region and their ability to bind and induce cellular responses (Heinsbroek et al. 2006).

Originally thought to be a dendritic cell-specific receptor, Dectin-1 is now known to be expressed by many other cell types such as monocytes, macrophages, neutrophils, and a subset of T cells (Taylor et al. 2002). Dectin-1 (βGR) is also expressed on B cells, eosinophils, and mast cells in humans, and recent reports have also demonstrated expression of this receptor on murine microglia (Olynych et al. 2006; Shah et al. 2008; Willment et al. 2005). Whether the differences in expression between species are functionally significant is currently unclear. Consistent with a potential role in immune surveillance, this receptor is prominently expressed at portals of pathogen entry such as the lung and intestine (Reid et al. 2004; Taylor et al. 2002). The levels of Dectin-1 expression can be significantly influenced by various factors such as steroids, some cytokines, and microbial stimuli. For example, IL-4, IL-13, and GM-CSF (granulocyte–macrophage colony-stimulating factor) cause significant upregulation of Dectin-1 expression. On the other hand, IL-10, LPS, and dexamethasone trigger downregulation of Dectin-1 expression (Willment et al. 2003). In addition, the systemic administration of *C. albicans* resulted in an increase in Dectin-1 expression on leukocytes. In contrast, Dectin-1 expression was decreased during polymicrobial sepsis (Ozment-Skelton et al. 2009).

Dectin-1 mediated fungal β-glucan recognition

A number of endogenous and exogenous ligands have been reported for Dectin-1, but this receptor is best known for its ability to recognize fungal β-glucans. β-Glucans are carbohydrate PAMPs found predominantly in fungal cell walls, but they are also present in plants and some bacteria. The β-glucan components of fungal cell walls consist primarily of (1→3)-β-D-linked polymer backbones with (1→6)-β-linked side chains of varying length and distribution (Romani et al. 2004; Tsoni and Brown 2008). These carbohydrates are well known for their anti-infective and antitumorogenic activities, and the identification of Dectin-1 as a PRR that recognizes β-glucans has enabled significant advances in our understanding of the mechanisms underlying these activities. A number of other receptors have also been implicated in β-glucan recognition, namely, complement receptor 3 (CR3), lactosylceramide, langerin, and the scavenger receptors CD5, CL-P1, SCARF1, and CD36 (de Jong et al. 2010; Jang et al. 2009; Means et al. 2009; Ross et al. 1987; Vera et al. 2009; Zimmerman et al. 1998). We and others have shown that Dectin-1 is the primary receptor for β-glucans, at least on leukocytes. However, it should be noted that the other receptors may have significant roles in mediating responses to β-glucans, particularly in nonimmune cells.

Initially identified as a receptor that recognized an unidentified ligand on T lymphocytes (Ariizumi et al. 2000), Dectin-1 was reidentified as a receptor for β-glucans following a screen of a murine macrophage cDNA expression library with zymosan, a β-glucan-rich extract of *S. cerevisiae* (Brown and Gordon 2001). Biochemical characterization of the interaction has shown that Dectin-1 is highly specific for (1→3)-linked β-glucans and that its

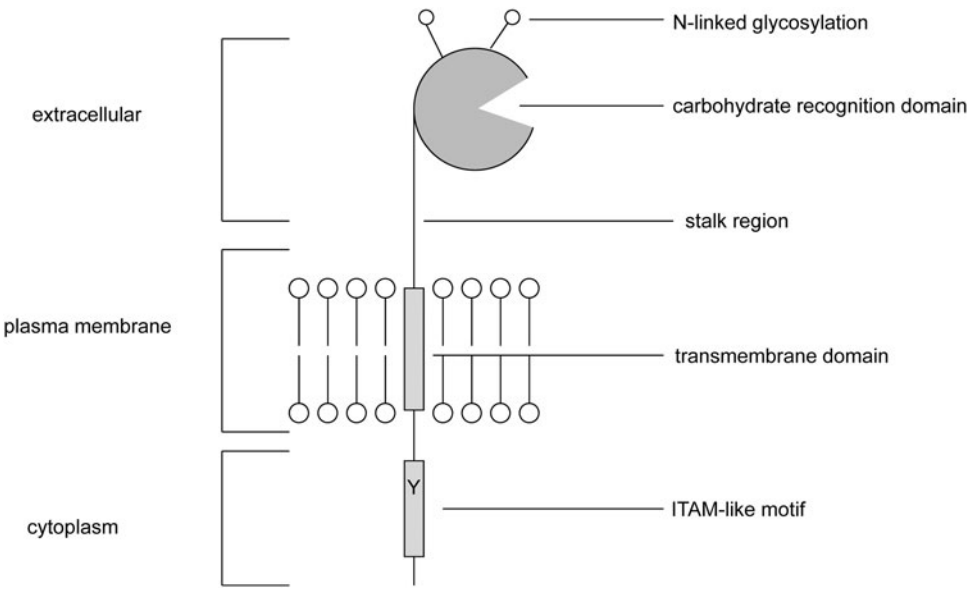

Fig. 1 A schematic representation of the structure of Dectin-1

binding affinity for these carbohydrates is influenced by factors such as polymer length and number of branches (Adams et al. 2008; Goodridge et al. 2009b; Palma et al. 2006). The manner in which Dectin-1 recognizes β-glucans is still unclear as its CTLD lacks the residues typically known for carbohydrate binding and ligand recognition is metal ion-independent. However, at least two residues flanking a shallow groove on the protein surface, Trp^{221} and His^{223}, have been implicated for β-glucan binding (Adachi et al. 2004).

Dectin-1 has been shown to interact with a number of fungal species, including *Candida*, *Pneumocystis*, *Saccharomyces*, *Aspergillus*, *Coccidioides*, and *Penicillum*, by way of its β-glucan specificity (Brown et al. 2003; Gantner et al. 2005; Gersuk et al. 2006; Nakamura et al. 2008; Saijo et al. 2007; Steele et al. 2003, 2005; Taylor et al. 2007; Viriyakosol et al. 2005). It has also been shown that Dectin-1 can recognize other nonfungal pathogens. For instance, a role for this receptor has been suggested in the recognition of mycobacteria (Lee et al. 2009; Rothfuchs et al. 2007; Shin et al. 2008; Yadav and Schorey 2006), which do not possess β-glucans, suggesting that there may still be unidentified exogenous ligands of Dectin-1 yet to be discovered.

Cellular responses induced by Dectin-1 following fungal β-glucan recognition

Dectin-1 recognition of β-glucans can result in the induction of a number of cellular responses, including ligand uptake by phagocytosis and endocytosis, dendritic cell maturation, the respiratory burst, the production of arachidonic acid metabolites, and the induction of numerous cytokines, including tumor necrosis factor (TNF), IL-10, IL-2, IL-23, and IL-6, as well as chemokines like CXCL2 (Brown 2006; Reid et al. 2009). In addition to triggering innate immune responses, ligation of Dectin-1 can also activate adaptive immune responses. For example, Dectin-1-mediated activation of dendritic cells in response to curdlan, a selective agonist of this receptor, has been shown to direct the differentiation of T-helper 17 (Th17) and T-helper 1 (Th1) $CD4^+$ T cells in vitro (LeibundGut-Landmann et al. 2007). Furthermore, curdlan acted as an adjuvant for the priming of Th17 and Th1 $CD4^+$ T cells in vivo (LeibundGut-Landmann et al. 2007). Dectin-1 has also been implicated in the expansion and function of regulatory T cells (Tregs) (Dillon et al. 2006; Karumuthil-Melethil et al. 2008), as well as in the conversion of selected populations of Tregs into IL-17, producing T cells that cannot be strictly classified as either Th17 cells or Tregs (Osorio et al. 2008). In addition, Dectin-1 signaling can induce $CD8^+$ T-cells responses, as demonstrated by in vivo studies that showed that curdlan was found to efficiently prime cytotoxic T-cell responses (Leibundgut-Landmann et al. 2008). Signaling induced via Dectin-1 alone can directly trigger some of these responses; however, other responses such as the production of proinflammatory cytokines require, or are enhanced by, collaborative signaling with TLRs (Brown et al. 2003; Dennehy et al. 2008; Gantner et al. 2003). Yet another element that adds to the complexity of Dectin-1 signaling was revealed by studies showing that the ability of β-glucans to directly trigger these responses is cell-type dependent (Goodridge et al. 2009a; Rosas et al. 2008). In the following section we review the current understanding of the Dectin-1-mediated signaling pathways that underlie some of these responses.

Dectin-1 intracellular signaling

Dectin-1 signaling is mediated by a sequence within the cytoplasmic tail that resembles an immunoreceptor tyrosine-based activation motif (ITAM). Traditional ITAMs present in T-cell receptors, B-cell receptors, and Fc receptors contain an amino acid sequence comprising duplicate YXXL/I motifs ($YXXL/IX_{6\text{-}12}YXXL/I$), where Y is tyrosine, L is leucine, I is isoleucine, and X denotes any amino acid. Phosphorylation of both tyrosines by Src family kinases is required for recruitment of Syk family kinases and subsequent downstream signaling (Underhill and Goodridge 2007). The cytoplasmic tail of Dectin-1 also contains two tyrosines: the membrane-proximal tyrosine is located in a YXXL motif and the membrane-distal one is found in a motif containing an additional amino acid (YxxxL and YxxxI in humans and mice, respectively) (Brown 2006). Dectin-1 also becomes tyrosine phosphorylated following ligand binding, but in contrast to traditional ITAM receptors, phosphorylation of only the membrane-proximal tyrosine is required for Dectin-1 signaling (Fuller et al. 2007; Rogers et al. 2005). This single-tyrosine-based motif (YxxL) is now known as an ITAM-like motif or a hemITAM. Dectin-1 was the first receptor shown to signal via this pathway, which although quite similar to ITAM signaling, is unique in its dependence on only a single tyrosine. Other receptors, specifically the C-type lectins CLEC-2 and CLEC-9A, have subsequently been shown to also signal via an ITAM-like motif (Fuller et al. 2007; Huysamen et al. 2008). Although the exact nature of the interaction between Syk and Dectin-1 is unclear, a model suggesting that Syk bridges two monophosphorylated molecules has been proposed (Brown 2006; Fuller et al. 2007; Goodridge et al. 2009b; Rogers et al. 2005). Indeed, experimental evidence strongly suggests that the related ITAM-like-containing receptor CLEC-2 regulates Syk through dimerization, with each of the Syk SH2 domains binding to a phosphorylated YxxL

sequence in the individual cytosolic tails of two CLEC-2 proteins (Hughes et al. 2010).

Ligand binding and the subsequent recruitment of Syk to Dectin-1 result in activation of PLCγ2, leading to the engagement of the caspase recruitment domain (CARD)-containing protein CARD9 (Gross et al. 2006; Tassi et al. 2009; Xu et al. 2009). CARD9, which then assembles with BCL10 and MALT1, has been identified as a key downstream adaptor required to link Dectin-1/Syk ligation to canonical NF-κB activation (Gross et al. 2006; Hara et al. 2007) (Fig. 2). Work by Gringhuis et al. (2009) also demonstrated Dectin-1 as the first PRR to induce noncanonical NF-κB activation. In addition, these authors showed that the stimulation of Dectin-1 with curdlan or *C. albicans* induced a second Syk-independent signaling pathway mediated by the serine-threonine kinase Raf-1. This pathway integrates with the Syk pathway at the point of NF-KB activation and might be involved in the pathogenesis of fungal infections (Gringhuis et al. 2009). Dectin-1 has also been shown to trigger NFAT activation, which regulates the induction of early growth response (Egr) family transcription factors Egr-2 and Egr-3 (Goodridge et al. 2007). Evidence also exists for Syk-dependent pathways that do not rely on CARD9 for cytokine production, e.g., activation of the MAP kinase ERK (Slack et al. 2007).

Dectin-1 in defense against fungal pathogens and effects of genetic polymorphisms/deficiency in mice and humans

Over the last few decades the growth of immunocompromised populations, such as individuals infected with HIV and transplant recipients, has resulted in an increased clinical relevance of fungal diseases. Thus, fungal research has attracted renewed interest, particularly efforts that seek to understand the mechanisms underlying protective immunity. In this section we discuss the role of Dectin-1 in antifungal immunity and highlight studies that demonstrate the consequences of Dectin-1 deficiency in fungal infections.

As mentioned previously, the recognition of fungal β-glucans by Dectin-1 results in a variety of cellular responses, some of which are host protective such as fungal uptake and killing, and the production of inflammatory cytokines and chemokines. Interestingly, Dectin-1 also induces the production of IL-10, an anti-inflammatory cytokine whose role during fungal infection is unclear. The presence of IL-10 has traditionally been thought of as disadvantageous to the host during fungal infection; however, recent investigations have led to the proposal that the inhibitory action of IL-10 on leukocyte activation may be important for limiting host damage during severe

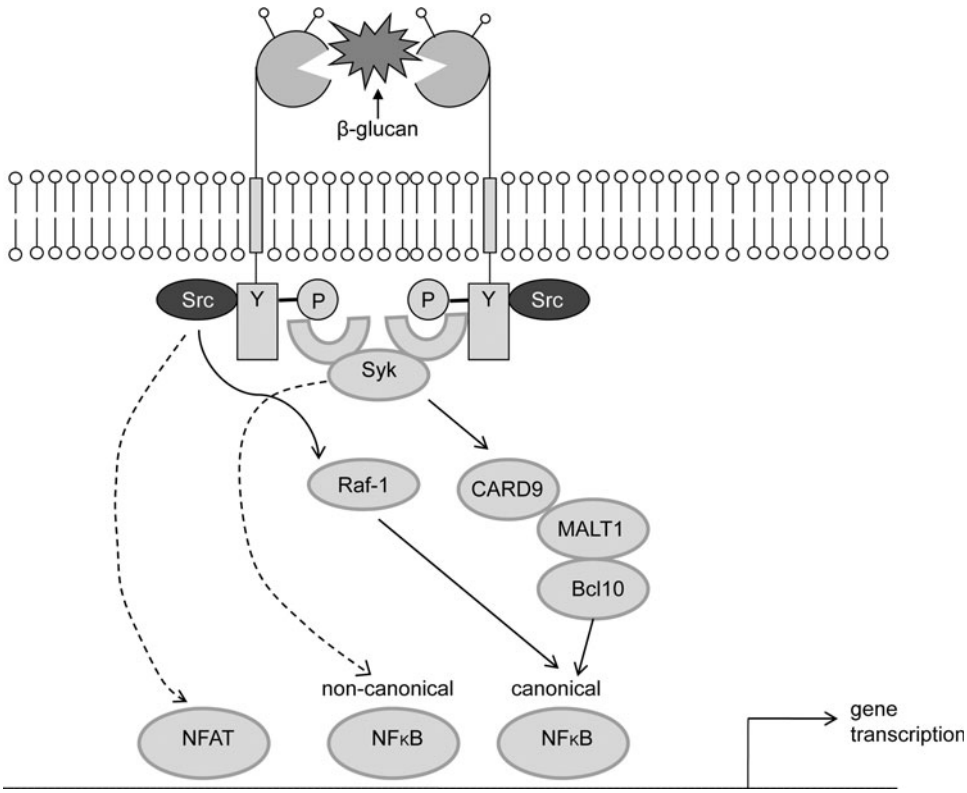

Fig. 2 Signaling pathway induced by Dectin-1. Upon ligand binding, Dectin-1 becomes tyrosine-phosphorylated by Src kinases, thereby providing a docking site for Syk which initiates downstream signaling. The downstream signaling is effected by molecules such as CARD9, Bcl10, and MALT1, which lead to NF-κB activation and cytokine production. Dectin-1 can also activate NFAT and noncanonical NF-κB in a CARD9-Bcl10-MALT1-independent manner. Stimulation of Dectin-1 with β-glucans can also induce a second Syk-independent signaling pathway mediated by the serine-threonine kinase Raf-1

inflammation (Romani and Puccetti 2006). It has also been shown that IL-10 is involved in the development of Tregs, whose modulatory actions are beneficial in mucosal and cutaneous infections and which are known to be essential for the induction of long-term immunity to *C. albicans* (Netea et al. 2004). In contrast, it has been proposed that in situations such as disseminated candidiasis, where the pathogen penetrates the mucosa and disseminates through the bloodstream, the presence of Tregs is detrimental to the host (Netea et al. 2004).

We have also mentioned that Dectin-1 can drive other aspects of adaptive immunity, including Th1, Th17, and CTL responses, although there have been no studies looking specifically at the roles of these Dectin-1-mediated responses in antifungal immunity. Nevertheless, it is generally accepted that a Th1 response is required for protection against fungal infection in healthy hosts (Romani 2004). On the other hand, whether a Th17 response is required for efficient antifungal immunity is a more contentious issue, with contradictory reports demonstrating Th17 cells as both beneficial and detrimental to the host during systemic infections with *Candida* (Bozza et al. 2008; Huang et al. 2004; Romani 2004; Saijo et al. 2010; Zelante et al. 2007). In contrast, Th17 cells are known to be important during mucosal infections with *Candida* (Conti et al. 2009). The specific role of CTLs in direct antifungal responses is also undefined; however, it has been shown that $CD8^+$ T cells are activated during fungal infections and can play a protective role in some cases (Leigh et al. 2006; Lindell et al. 2005; Marquis et al. 2006; Wuthrich et al. 2003).

Interestingly, Dectin-2, another Syk/CARD9-coupled CLR, has also been shown to mediate dendritic cell activation and induction of Th17 immunity in response to *C. albicans* (Robinson et al. 2009). Furthermore, in the final stages of writing this review, an investigation using Dectin-2-deficient mice reported that this receptor was important in host defense against systemic *C. albicans* in mice (Saijo et al. 2010).

It is important to note that fungal morphology is a major determinant in the detection of cell wall β-glucans, as the exposure of these carbohydrates can vary from one fungal morphotype to another. For example, it has been shown that Dectin-1 recognizes *C. albicans* yeast but not filamentous forms (Gantner et al. 2005). Thus, the ability of *C. albicans* to switch between different forms may be a key virulence strategy to evade host immune responses (Calderone and Fonzi 2001; Lo et al. 1997; Saville et al. 2003). In fact, *C. albicans* mutants that lack the ability to switch from yeast to filamentous forms have been reported to be avirulent in mouse models (Lo et al. 1997). In *A. fumigatus*, swollen conidia and early germlings displaying surface β-glucans are recognized by Dectin-1, hyphal forms are recognized to a lesser degree, and resting conidia are not recognized (Gersuk et al. 2006; Hohl et al. 2005; Steele et al. 2005; Torosantucci et al. 2005). It has also been suggested that fungal pathogens actively mask their β-glucans to avoid immune recognition by Dectin-1 (Gantner et al. 2005; Wheeler and Fink 2006), prompting investigations into drugs, such as caspofungin, which enhance the exposure of β-glucans and improve antifungal responses (Hohl et al. 2008; Lamaris et al. 2008; Wheeler and Fink 2006; Wheeler et al. 2008).

Increasing evidence from in vivo studies, although not entirely consistent, suggests an important role for Dectin-1 in antifungal immunity. Studies in our laboratory have shown that the deletion of *Clec7a*, the gene encoding Dectin-1, significantly increased susceptibility of mice to systemic infection with *C. albicans* (Taylor et al. 2007). Loss of Dectin-1 in this model resulted in increased fungal burdens and much lower survival times. A peritoneal infection model revealed that the Dectin-1 knockout mice had fewer recruited cells than wild types, including neutrophils and inflammatory monocytes, which correlated with defects in the production of cytokines and chemokines such as TNF, IL-6, CCL2, CCL3, and GM-CSF. This study suggested a fundamental role of β-glucan recognition by Dectin-1 in antifungal immunity and the requirement for Dectin-1-dependent signaling for the induction of protective immune responses (Taylor et al. 2007). In contrast to this study, Saijo et al. showed that Dectin-1-deficient mice were not more susceptible than wild-type mice to infection with *C. albicans* (Saijo et al. 2007). We suspect that the inconsistencies between these two studies arose as a result of the use of different fungal strains.

Nevertheless, other studies have supported a role for Dectin-1 in antifungal immunity. In a model of oral candidiasis, Dectin-1-deficient mice showed increased susceptibility, with enhanced dissemination and decreased survival times (Hise et al. 2009). Furthermore, mice deficient in the downstream signaling component CARD9 were similarly more susceptible to systemic *C. albicans* infection (Gross et al. 2006). Dectin-1 is also required during infection with other fungal pathogens; e.g., Dectin-1-deficient mice displayed increased susceptibility to *A. fumigatus* infection which correlated with impaired cytokine production and fungal killing (Steele et al. 2005; Werner et al. 2009). Furthermore, in a model of intranasal infection with *Pneumocystis carinii*, Dectin-1-deficient mice were found to be more susceptible than wild-type mice in the early stages of infection (Saijo et al. 2007).

Recently, an investigation by Ferwerda et al. provided definitive evidence of the role of Dectin-1 during fungal infections in humans. This study identified and described a polymorphism of human Dectin-1 in four members of a Dutch family who were affected by either recurrent

vulvovaginal candidiasis or onychomycosis (fungal infection of the nail), or both (Ferwerda et al. 2009). The polymorphism was characterized by an early-stop-codon mutation (Y238X) in the CTLD of Dectin-1, resulting in defective expression and lack of β-glucan recognition by phagocytes. In addition, the mutation resulted in impaired production of cytokines, including IL-17. However, the uptake and killing of *C. albicans* by neutrophils was not affected. This suggests that alternative receptor pathways can mediate these activities in the absence of Dectin-1, and this is likely to provide protection against systemic fungal infection in these individuals (Ferwerda et al. 2009).

This study also indicated that there are gene-dose effects associated with the Y238X mutation. For example, the homozygous daughters were 10-12 years of age at onset of symptoms, but the heterozygous mother and father were 40 and 55 years of age, respectively. Furthermore, heterozygotes had an intermediate production of proinflammatory cytokines upon stimulation with *C. albicans* or β-glucan and were statistically significantly more often colonized with *C. albicans* than patients with wild-type Dectin-1 (Plantinga et al. 2009). In terms of the frequency of the mutation, analysis indicated its presence only in populations from Africa and western Eurasia (allele frequency of 3-7%), with the highest prevalence (nearly 40%) found in the San population in South Africa (Ferwerda et al. 2009).

Plantinga et al. also investigated the association of the Dectin-1 polymorphism with *C. albicans* colonization in patients undergoing hematopoietic stem cell transplantation (HSCT) (Plantinga et al. 2009). Treatment of patients who have hematological malignancies with HSCT is accompanied by a high incidence of invasive fungal infections which cause considerable morbidity and mortality (Barnes and Marr 2007). The study by Plantinga et al. demonstrated that the Y238X Dectin-1 polymorphism is associated with increased susceptibility to oral and gastrointestinal colonization with *Candida* species in HSCT recipients (Plantinga et al. 2009). These findings affirm the importance of Dectin-1 in protection against fungal infections in immunocompromised patients, including those undergoing transplantation. The authors propose the implementation of an approach in which patients with the polymorphism are considered for antifungal prophylaxis to help prevent systemic candidiasis.

A further study investigated whether the Dectin-1 early-stop-codon polymorphism could have an impact on the immunological response following transplantation (van der Velden et al. 2010). The authors specifically screened for association between the Dectin-1 polymorphism and the incidence of graft-versus-host disease (GvHD) following stem cell transplantation. This study found that in patients colonized with *Candida*, the presence of the Dectin-1 polymorphism reduced the incidence of acute GvHD. Interestingly, recent studies have suggested a role for Th17 responses in the pathogenesis of GvHD (Carlson et al. 2009; Elmaagacli et al. 2008; Kappel et al. 2009). Considering that *C. albicans* is known to induce Th17 responses in mice and humans, the authors suggest that the link between *Candida* colonization and acute GvHD may be the induction of Th17 responses by the fungus (van der Velden et al. 2010). Their results suggest that despite increased colonization, defective Dectin-1 signaling prevented an increase in Th17-mediated acute GvHD. This study therefore established a link between *Candida* colonization and acute GvHD in humans.

As discussed previously, CARD9 is a major component of the downstream signaling pathway of Dectin-1, and recently Glocker et al. (2009) described a mutation causing a loss of function of CARD9 that was associated with an increased susceptibility to chronic mucocutaneous candidiasis. In addition, the CARD9$^{-/-}$ patients had significantly reduced numbers of Th17 cells. This study further supports the role of Dectin-1/Syk/CARD9 signaling in the differentiation of Th17 cells and in antifungal immunity.

Dectin-1 polymorphisms in other human diseases

The effects of Dectin-1 polymorphisms have also been studied in other human diseases and are briefly described here. First, Dectin-1-mediated responses have been implicated in driving autoimmunity. Fungal particles such as zymosan and β-glucans can induce inflammation and autoimmune arthritis in mice, and Yoshitomi et al. (2005) have shown that blocking Dectin-1 prevented β-glucan-induced autoimmune arthritis in genetically susceptible mice. Therefore, in order to determine if Dectin-1 is associated with rheumatoid arthritis (RA) in humans, Plantinga et al. (2010) investigated clinical parameters of inflammation and bone destruction in arthritis patients, including those bearing the heterozygous Dectin-1 polymorphism. This study showed that partial Dectin-1 deficiency had no association with disease susceptibility or with the degree of inflammation and bone destruction in RA patients.

Mutations in *CARD9* have been associated with inflammatory bowel disease (IBD) (Zhernakova et al. 2008), and consequently the involvement of the Dectin-1 polymorphism in IBD was also investigated. Although Dectin-1 expression was found to be elevated on macrophages, neutrophils, and other cells involved in the inflammatory reaction in IBD lesions, the Dectin-1 polymorphism was found not to be a major susceptibility factor for the development of this disease (de Vries et al. 2009).

Conclusion

The discovery of Dectin-1 has revolutionized our understanding of molecular mechanisms underlying innate recognition of fungi. The study of this receptor has revealed novel insights into the intracellular signaling pathways and cellular responses induced by fungal β-glucans. Definitive evidence for its protective role in fungal disease has come from studies of patients harboring a Dectin-1 polymorphism that results in defective expression of the protein. Finally, given the current clinical evidence for the role of this receptor in fungal diseases, looking at ways of restoring the defective responses that are normally induced by Dectin-1 may provide new avenues for therapeutic intervention.

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